Clinical Biochemistry 48 (2015) 302–307

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

High-sensitive cardiac troponin, NT-proBNP, hFABP and copeptin levels in relation to glomerular filtration rates and a medical record of cardiovascular disease

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ARTICLE INFO

Article history:
Received 22 June 2014
Received in revised form 21 December 2014
Accepted 12 January 2015
Available online 28 January 2015

Keywords:
Cardiac biomarkers
Cardiac troponin
Kidney function

ABSTRACT

Background: Elevation of cardiac markers in patients with renal dysfunction has not been fully assessed reducing the diagnostic usefulness of these biomarkers.

Objective: To examine the effects of renal function and a medical record of cardiovascular disease on levels of cardiac biomarkers.

Methods: Serum samples were collected from 489 patients referred for GFR measurement using Cr51-EDTA or iohexol plasma clearance (measured GFR). The cardiac biomarkers Troponin T (hs-cTnT), Troponin I (hsTnI), N-Terminal pro-Brain Natriuretic Peptide (NTproBNP), Copeptin, Human Fatty Acid-Binding Protein (hFABP), as well as the kidney function biomarkers creatinine and cystatin C, were measured. Regression was used to analyse the relationship between biomarker levels and the glomerular filtration rate (GFR) between 15 and 90 mL/min/1.73 m^2.

Results: Compared with normal kidney function, the estimated increases in the studied cardiac biomarkers at a GFR of 15 mL/min/1.73 m^2 varied from 2-fold to 15-fold but were not very different between patients with or without a medical record of cardiovascular disease and were most prominent for cardiac biomarkers with low molecular weight. hs-cTnT levels correlated more strongly to measured GFR and increased more at low GFR compared to hs-cTnI. For hFABP and NTproBNP increases at low kidney function were more correctly predicted by a local Cystatin C-based eGFR formula compared with creatinine-based eGFR (using the MDRD or CKD-EPI equations).

Conclusion: The extent of the elevation of cardiac markers at low renal function is highly variable. For hFABP and NTproBNP Cystatin C-based eGFR provides better predictions of the extent of elevation compared to the MDRD or CKD-EPI equations.

Introduction

The diagnosis of cardiac disease, such as heart failure and myocardial infarction, often involves cardiac damage biomarkers such as cardiac troponin T (cTnT), cardiac troponin I (cTnI) [1,2], and human fatty acid-binding protein (hFABP) [3,4]. In addition, hormones secreted in response to cardiac stress, such as brain natriuretic peptide (BNP) and anti-diuretic hormone (ADH), also provide diagnostic and prognostic information in heart failure and myocardial infarction. The production of BNP and ADH is generally estimated on the basis of the circulating levels of N-Terminal pro-Brain Natriuretic Peptide (NTproBNP) [5,6] and Copeptin [7–11], apparently inactive peptides that are secreted in equimolar amounts together with the active stress hormones.

Cardiovascular disease is common among patients with renal insufficiency [12]. It is well known that cardiac biomarkers are often increased in patients with impaired renal function due to decreased clearance, as a part of the cardio-renal syndrome, uraemic cardiotoxins [12] or a combination [13,14] of these factors. However, the extent of elevation expected at a given glomerular filtration rate (GFR) is not well examined for most cardiac biomarkers. This impairs the diagnostic

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http://dx.doi.org/10.1016/j.clinbiochem.2015.01.008

precision in patients with poor renal function and suspected cardiac disease, especially in the acute setting [15].

Renal function is often not measured directly via Cr^{51}-EDTA or iohexol plasma clearance (measured GFR) [16], but estimated on the basis of the levels of endogenous filtration biomarkers, such as creatinine or cystatin C. Creatinine and Cystatin C are produced at a relatively constant rate and are, for the most part, cleared via renal filtration. Steady-state concentrations of creatinine and cystatin C therefore reflect renal filtration rate and can be used to estimate GFR (eGFR) [17]. It is still debated if eGFR calculated using creatinine or cystatin C levels more closely predict measured GFR and GFR-related outcomes [18,19].

We have examined the extent of elevation of common cardiac biomarkers in stable patients with a known GFR. We have also evaluated whether the eGFR, calculated from a local cystatin C-based equation, and creatinine, calculated using the MDRD or CKD-EPI equations, differ in their ability to predict elevations of cardiac biomarkers in patients with poor kidney function.

Methods

Study cohort

This study included 489 patients prospectively referred for measurement of Cr51-EDTA or iohexol clearance [7] at the Department of Clinical Physiology, Sahlgrenska University Hospital, Gothenburg, Sweden, during 2009–2011, who agreed to participate in the study. Medical records were reviewed, especially if the patients had high levels of cTnT and other cardiac biomarkers. Based on this review, 29 patients were excluded due to serious illness that was judged as the major reason for the biomarker elevation by a physician. The reasons for exclusion are listed in Supplemental Fig. 1. The remaining 460 patients were divided based on the presence (n = 223) or absence (n = 237) of cardiovascular disease, as determined by the presence or absence of an ICD10 diagnosis code beginning with the letter I, such as atrial fibrillation (I489, I489A, I489B), heart failure (I500, I501, I509), CIHD, old myocardial infarction and angina (I259, I258, I228, I229, I252, I209). Ten patients lacked available diagnostic codes and were not included in analyses of patients with and without cardiovascular disease and were thus only present in the analysis of all patients. The study protocol was approved by the Ethical Committee at the University of Gothenburg. Written informed consent was obtained from all patients and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Laboratory analyses

One or two-point iohexol plasma clearance or Cr^{51}-EDTA plasma clearance was used to measure GFR (measured GFR). The relative performance of these routine methods has been evaluated by simultaneous injection of Cr^{51}-EDTA and iohexol in the same patients and the two methods were found to generate similar results [16]. Blood sampling was carried out at the same time as GFR measurement. Serum was stored at −70 °C before analysis. All blood samples were analysed at the Clinical Chemistry Laboratory at Sahlgrenska University Hospital. The coefficient of variation (CV) calculated based on 12 repeated analysis on 3 consecutive days on the Roche's COBAS methods were; creatinine (CV 2.1%), Cystatin C (CV 1.7%), NTproBNP (CV 4.9%), and hs-TnT (3.3%). The coefficient of variation (CV) calculated based on 12 repeated analysis on 3 consecutive days were; hFABP (CV 1.3%, Randox), Copeptin (CV 4.1%, Brahms) and hs-TnI (CV 6.9%, Abbot). Further information on the methods are summarised in Supplemental Table 1. The estimated Glomerular Filtration Rate (eGFR) was calculated using demographics and creatinine concentrations according to the Modification of Diet in Renal Disease Study (MDRD) formula [20] or CKD-EPI [21]. The eGFR based on CysC was calculated using a locally generated equation (GFR (mL/min/1.73 m^2) = (85.47/CysC (mg/L)) − 9.64). This equation was was based on linear regression from Cystatin C concentrations and measured GFR using Cr51-EDTA or iohexol plasma clearance. The data and more details are included in supplementary figure 2. The CVs were calculated. The slope and the performance of this equation are summarised in Supplemental Figure 2.

Statistical analysis

Univariate comparisons between GFR groups were calculated using independent samples median tests (in Table 1 and Supplemental Table 2–3). Dichotomous variables were analysed using exact tests with Monte Carlo methods (in Table 1 and Supplemental Table 2–3). Functions to predict fold increases were identified using regression analyses on logarithmised levels of biomarkers used as dependent variables and logarithmised measured GFR values used as independent variables on patients with a measured GFR of ≥15 mL/min/1.73 m^2. The resulting mean functions (Log(Y) = a + b Log(X)) were used to calculate the estimated increase in each cardiac biomarker at a measured GFR of 60, 30 and 15 mL/min/1.73 m^2, using cardiac biomarker levels (estimated from the mean functions) at a measured GFR of 90 mL/min/1.73 m^2 as the reference. These regressions were also performed using eGFR from creatinine (calculated from the MDRD or CKD-EPI equations) and cystatin C (calculated from the local cystatin C equation) as the independent variable for each cardiac biomarker. To compare fold increases between different biomarkers Friedman tests and related samples Wilcoxon rank tests were used on actual biomarker levels among patients with GFR between ≥15 and <30 mL/min/1.73 m^2 after division by the median levels among patients with ≥GFR 90 mL/min/1.73 m^2. Fold increases between patients with and without I-diagnoses were compared using independent-samples median tests on the above described ratios. The ability of MDRD eGFR and CKD EPI eGFR to predict biomarker levels compared to cysC eGFR was analysed with related samples Wilcoxon rank tests. The absolute differences between actual biomarker levels and estimates from the respective mean functions (Log(Y) = a + b Log(X)) were then compared. Statistical analyses and calculations were performed using the SPSS version 20, MedCalc 13 and Microsoft Excel 2010. All tests were two-tailed, and p values < 0.05 were regarded as significant.

Results

Study population

The 460 patients admitted for measurement of GFR (by either Cr51-EDTA or iohexol clearance) and included in the study (Supplemental Fig. 1) had a median age of 58 (IQR 45–65) years and 56% were males. Biomarker levels and the percentages with CVD and diabetes in the medical record were higher among patients with a low GFR (Table 1). Therefore, patients with (n = 223) and without (n = 227) CVD in the medical record were also analysed separately (Supplemental Table 2 and 3). All studied cardiac biomarkers increased in a GFR-dependent manner in both cohorts but were higher in the CVD cohort at low measured GFRs ($p < 0.05$ for all studied biomarkers at GFR ≥ 15 and <60). The frequency of different CVD diagnoses, such as heart failure, was the same over the GFR quartiles in the CVD cohort (Supplemental Table 2).

Regression analysis of cardiac biomarker levels at different measured GFRs

Mean functions from regression analyses of cardiac biomarker levels and measured GFRs (Fig. 1) were used to calculate the fold increase in each biomarker at measured GFRs of 15, 30, and 60 mL/min/1.73 m^2, compared with the levels in patients with normal kidney function (90 mL/min/1.73 m^2) (Table 2). The regression analysis only included data from patients without renal failure, (GFR ≥ 15 mL/min/1.73 m^2),

Table 1
Baseline characteristics for all patients included in the study.

Measured GFR	GFR < 15[a]	GFR ≥ 15 and <30[a]	GFR ≥ 30 and <60[a]	GFR ≥ 60 and <90[a]	GFR > = 90[a]	P value
n = 460	30	54	146	148	80	
GFR (mL/min/1.73 m^2)						
Measured GFR	12 (10–13)	23 (17–26)	44 (36–51)	73 (65–81)	99 (95–105)	<0.001
CysC eGFR	10 (8–13)	21 (17–24)	39 (31–46)	62 (53–68)	79 (71–93)	<0.001
MDRD eGFR	14 (11–17)	28 (23–34)	48 (40–60)	77 (68–94)	99 (87–116)	<0.001
CKD EPI eGFR	12 (8.8–17)	26 (21–36)	50 (36–67)	87 (63–101)	102 (80–115)	<0.001
Renal function markers						
CysC (mg/L)	3.3 (2.9–3.6)	2.3 (2.1–2.6)	1.5 (1.3–1.8)	1.0 (0.96–1.2)	0.86 (0.75–0.93)	<0.001
Creatinine (mmol/L)	350 (309–459)	193 (155–238)	118 (97–147)	79 (66–94)	67 (55–76)	<0.001
Cardiac biomarkers						
hs-cTnT (ng/L)	41 (25–59)	21 (12–37)	15 (10–21)	9.4 (7.5–14)	7.1 (5.8–10)	<0.001
hs-cTnI (ng/L)	16 (11–27)	11 (7,5–19)	7.6 (5.1–11)	5.0 (4.1–6.8)	4.6 (3.3–7.1)	<0.001
NTproBNP (ng/L)	759 (352–2686)	789 (253–1790)	185 (87–471)	121 (51–271)	48 (27–93)	<0.001
Copeptin (pmol/L)	77 (56–89)	35 (24–47)	17 (10–27)	9 (5–14)	6 (4–9)	<0.001
hFABP (mg/L)	20 (16–23)	10 (8,2–14)	6.2 (4.8–8.2)	3.5 (2.9–4.4)	2.6 (2.1–3.3)	<0.001
Clinical variables						
Age	62 (53–70)	61 (53–69)	61 (50–67)	54 (42–64)	47 (35–57)	<0.001
Sex (males)	73%	61%	58%	53%	55%	0.30
Comorbidity						
I diagnosis	90%	70%	60%	38%	23%	<0.001
IHD	21%	15%	8%	6%	1%	0.004
AF	14%	11%	6%	2%	4%	0.03
Heart failure	17%	8%	8%	3%	1%	0.009
Hypertension	66%	43%	42%	21%	10%	<0.001
Diabetes	45%	21%	19%	8%	4%	<0.001
Stroke	0%	4%	2%	2%	1%	0.82
COPD	0%	2%	3%	2%	1%	0.75

AF: Atrial fibrillation; COPD: chronic obstructive pulmonary disease; CysC: Cystatin C; eGFR: estimated glomerular filtration rate (mL/min/1.73 m^2); GFR: glomerular filtration rate (mL/min/1.73 m^2); HFabp: Human Fatty Acid Binding Protein; hsTnI: high-sensitivity Troponin I; hs-cTnT: high-sensitivity cardiac Troponin T; I-diagnosis: ICD-10 code beginning with I; IHD: Ischemic heart disease; MDRD: Modification of Diet in Renal Disease Study; NTproBNP: N-Terminal pro Brain Natriuretic Peptide.
[a] Data is presented as medians (interquartile ranges) or proportions.

as almost all patients with renal failure had a CVD diagnosis in the medical record. Levels of all studied biomarkers were significantly higher at low GFR (Table 1 and 2). The association between GFR and biomarker levels was strong for hFABP (R^2 0.57 CI 0.51–0.63) but the association was poor (R^2 < 0 .35) for cTnI, cTnT and NTproBNP (Supplemental Table 4). In the entire study cohort and among patients with CVD in the medical record, hs-cTnT levels had a stronger association to measured GFR compared to hs-cTnI with no overlap in the coefficient of determination (R^2) confidence interval (Supplemental Table 4). The increase in studied cardiac biomarkers at a GFR of 15 mL/min/1.73 m^2, compared with normal kidney function, varied from 2.9-fold to 15-fold and was not significantly different for patients with or without CVD in the medical record except for hs-cTnT (p = 0.007) (Table 2). The regression-estimated increase of hs-cTnT was significantly higher at low measured GFR compared to hs-cTnI (Table 2).

Regression analysis of cardiac biomarker elevation using creatinine and cystatin C-based eGFR

Regression analyses of cardiac biomarker levels and cystatin C-based eGFR (using the local cystatin C equation) and creatinine based eGFR (using the MDRD or CKD-EPI equations) were compared (Table 3). Projected increases using cystatin C-based eGFR for all five studied cardiac biomarkers were significantly closer to the actual values in each patient compared to predictions using MDRD and for hFABP and NTproBNP using CKD-EPI (supplemental table 4). Regressions using the local cystatin C equation resulted in significantly higher coefficient of determination (R^2) compared with the MDRD equation for hs-cTnT and hFABP (Supplemental Table 4).

Discussion

In this study we have attempted to estimate GFR-dependent elevations of five commonly used cardiac biomarkers (hs-cTnI, hs-cTnT, NTproBNP, hFABP and copeptin) in stable patients with varying kidney function. These types of studies are problematic, as the increase in the levels of cardiac biomarkers is expected to be a combination of decreased clearance, increased production due to the cardio-renal syndrome and the fact that cardiac disease is more common among patients with poor kidney function. With these limitations in mind, some conclusions may still be drawn from our study.

Firstly, the GFR-dependent levels of cTnT and NTproBNP in our study were in agreement with those in previous studies [22–25]. Similar to previous studies, we find that the association between measured GFR and NTproBNP and cTnT was poor, with an R^2 of less than 0.35, in contrast with the strong association between measured GFR and the classical kidney function biomarkers creatinine and cystatin C. Similar to a previous study we found that the levels of cTnI were less affected by GFR compared with the levels of cTnT [26].

Secondly, cardiac biomarkers with a molecular weight below 25 kDa, and therefore expected to have a relatively free passage through the glomerular filtration membrane, such as NTproBNP, copeptin and hFABP, showed a more pronounced increase at low measured GFRs compared with cTnT and cTnI (p < 0.05 by Friedman mean ranks test), which have molecular weights above 25 kDa. Thus, our study indicates that renal function is a less important clearance mechanism for cTnT and cTnI compared with NTproBNP, hFABP and copeptin.

It is, however, important to note that the dominant clearance mechanism for any of the studied biomarkers is not fully known. For instance, the renal extraction index, the difference in the NTproBNP concentration in blood from the renal artery and the renal vein is close to its maximum value of 0.2 in patients [27]. However, although NTproBNP is cleared by the kidneys [28], several studies indicate that NTproBNP elevations often observed in patients with poor kidney function are likely a reflection of increased production from the heart [29]. For instance, the levels of NTproBNP have a preserved ability to predict the heart failure diagnosis and prognosis in patients with poor kidney function without adjustment for GFR [30,31]. Therefore, although NTproBNP is cleared

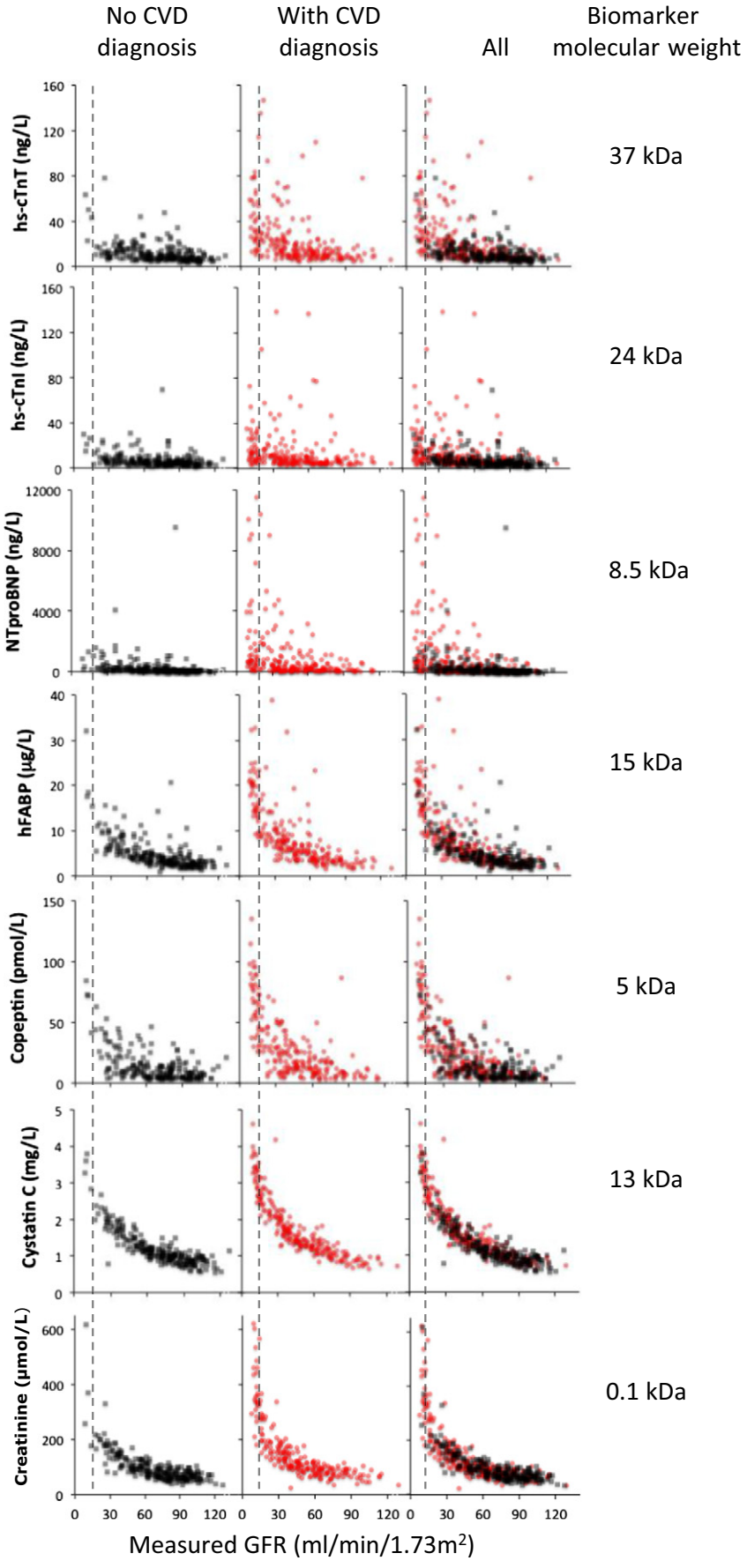

Fig. 1. Dot-plot presentation of the data used in the regression analyses using measured GFR (either by Cr51-EDTA or iohexol clearance). The dotted lines indicate renal failure (measured GFR of 15 mL/min/1.73 m^2).

Table 2
Fold elevation[a] of cardiac biomarkers at different levels of GFR compared with normal kidney function.

	All				With CVD diagnosis				No CVD diagnosis			
Measured GFR (mL/min/1.73 m^2)	90	60	30	15	90	60	30	15	90	60	30	15
hs-cTnT	1	1.3	2.2	3.6[bc]	1	1.3	2.2	3.7[d]	1	1.2	1.7	2.4[d]
hs-cTnI	1	1.3	1.9	2.9[bc]	1	1.2	1.6	2.2	1	1.2	1.7	2.3
NTproBNP	1	1.9	5.3	15.2[b]	1	1.7	4.1	9.9	1	1.8	4.7	12.4
Copeptin	1	1.5	3	6.1[b]	1	1.5	3	5.9	1	1.4	2.6	4.9
hFABP	1	1.4	2.7	5.1[b]	1	1.4	2.7	5.1	1	1.3	1.9	2.8

CysC: Cystatin C; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; HFabp: Human Fatty Acid-Binding Protein; hs-cTnT: high-sensitivity cardiac Troponin T; MDRD: Modification of Diet in Renal Disease Study; hsTnI: high-sensitivity Troponin I; NTproBNP: N-Terminal pro-Brain Natriuretic Peptide.
[a] Based on regression analyses using biomarker levels and measured GFR.
[b] Difference in fold elevation: hs-cTnI < hs-cTnT < hFABP < Copeptin < NTproBNP by Friedman mean ranks test ($p < 0.001$).
[c] Fold elevation: hs-cTnI < hs-cTnT by Wilcoxon Signed Rank Test ($p < 0.001$).
[d] Higher elevation of hs-cTnT in patients with CVD compared to patients without CVD by independent samples median tests ($p = 0.007$).

by renal filtration, these studies indicate that extra-renal clearance dominates for NTproBNP. An example of this is myoglobin that has a free passage through the glomerular membrane (18 kDa) but still have the same half-life in patients with or without impaired kidney function [32–34], suggesting a major role for extra-renal clearance. The exact mechanisms of the extra-renal clearance of these proteins and peptides are unknown but likely involve proteolytic degradation and scavenger receptor-mediated uptake in the liver and macrophages [35].

Thirdly, the levels of the five cardiac biomarkers were generally higher in patients with CVD in their medical records. This was likely a result of the increased production in patients with CVD. For instance, left ventricular mass and hypertension are GFR-independent predictors of the cTnT levels in patients with chronic kidney disease, probably due to increased cTnT release from the heart in these conditions [23]. In addition, the prognostic impact of elevated NTproBNP, cTnT, MRproANP, MRproADM and copeptin in patients with heart failure is independent of renal function, indicating that increased production rather than decreased renal clearance is the dominating reason for the observed elevation at low GFR [31].

Because the levels of the studied cardiac biomarkers were higher among patients in the CVD cohort, also at normal kidney function, the relative GFR-dependent increase in cardiac biomarkers was similar in cohorts with or without CVD in the medical record. Therefore, although the absolute levels of the studied cardiac biomarkers were higher in patients with CVD in the medical record, the relative GFR-dependent increase was similar in the cohorts with and without CVD in the medical record. The fact that the relative frequency of different cardiovascular diseases was the same at different GFR levels in the CVD cohort likely contributed to this effect.

As discussed above, it is unclear in our study, as in most similar studies [22,23,31], to which extent the increased production or decreased kidney clearance contributed to the increases in cardiac biomarker levels observed among patients with a low GFR. A possible exception was the level of hFABP, which did not differ much between patients with or without CVD and showed the highest association to measured GFR with a R^2 that overlapped with the confidence interval for the R^2 for creatinine. This indicates that decreased renal clearance contributed to the GFR-dependent elevations of hFABP.

Lastly, our study indicates that using a locally generated formula for cystatin C-based eGFR result in better predictions of GFR-dependent increases, at least for hFABP and NTproBNP, compared with creatinine-based predictions (Table 3). This could be due to the fact that cystatin C-based eGFR often outperform creatinine as a method to estimate GFR [36]. In line with this possibility, cystatin C levels are more strongly correlated with cardiovascular disease and mortality than creatinine levels in several studies [37–40].

However, although not significant, we observed that the cystatin C-based eGFR often correlated to a higher degree with our studied cardiac biomarker levels than the measured GFR (Supplemental Table 2). It is therefore possible that conditions that result in an increased production of cardiac biomarkers, such as the cardio-renal syndrome, also increase the cystatin C production. In line with this possibility, cystatin C was shown to be a predictor of the prognosis in ischemic cardiovascular disease in patients with a normal GFR [41], and was a better predictor of cardiovascular death compared with the measured GFR in patients with chronic kidney disease [42].

A limitation of this study was that the cardiac function of the participants was not systematically evaluated and only based on information in medical records. As a result, left ventricular mass that has been shown to correlate with the cTnT and NTproBNP levels in patients with kidney failure [23,24] was not systematically evaluated. Another problem was that the study cohort was not composed of a specific patient group. Potential strengths are the multitude of biomarkers measured simultaneously, allowing direct comparison of their association with GFR. In addition, and in contrast with many previous studies, GFR was measured directly with Cr51-EDTA or iohexol in all patients.

In conclusion, this study provides estimates of the extent of elevation of several important cardiac biomarkers at low renal function (Table 2) and indicates that estimates using cystatin C is better than estimates using creatinine at least for hFABP and NTproBNP (Table 3).

Table 3
Comparison of the ability of MDRD eGFR or CKD EPI eGFR versus CysC eGFR to predict biomarker levels.

Biomarker	CysC eGFR versus MDRD eGFR	CysC eGFR versus CKD EPI eGFR
hs-cTnT	$p < 0.001$[a]	$p = 0.22$
hs-cTnI	$p < 0.001$[a]	$p = 0.41$
NTproBNP	$p < 0.001$[a]	$p < 0.001$[a]
Copeptin	$p < 0.001$[a]cih	$p = 0.61$
Hfabp	$p < 0.001$[a]	$p < 0.001$[a]

CysC: Cystatin C; eGFR: estimated glomerular filtration rate; HFabp: Human Fatty Acid-Binding Protein; hs-cTnT: high-sensitivity cardiac Troponin T; MDRD: Modification of Diet in Renal Disease Study; hsTnI: high-sensitivity Troponin I; NTproBNP: N-Terminal pro-Brain Natriuretic Peptide.
[a] Predictions by CysC significantly better with related samples Wilcoxon rank tests.

Competing interests

None.

Funding

This study was supported by the Heart and Lung Foundation (grant number 20130490), Swedish Cancer Society, The Swedish Pain Foundation (SSF), and LUA/ALF Funding at the Sahlgrenska University Hospital.

Ethics

The study protocol was approved by the Ethical Committee at the University of Gothenburg. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Data sharing

No additional data are available.

Contributorship Statement

The five authors are justifiably credited with authorship, according to the authorship criteria. In detail: CB and JF — conception, design, acquisition of data, analysis and interpretation of data, drafting of the manuscript and final approval; MP — analysis and interpretation of data, statistical assistance and final approval; OH and MF — interpretation of data, drafting of the manuscript and final approval.

Acknowledgements

We are grateful for the expertise and analysis of the laboratory parameters by the staff at the department of Clinical Chemistry at Sahlgrenska University Hospital.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.clinbiochem.2015.01.008.

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